

IS RESPIRATION-INDUCED VARIATION IN THE PHOTOPLETHYSMOGRAM ASSOCIATED WITH MAJOR HYPOVOLEMIA IN PATIENTS WITH ACUTE TRAUMATIC INJURIES?

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ABSTRACT—It has been widely accepted that metrics related to respiration-induced waveform variation (RIWV) of the photoplethysmogram (PPG) have been associated with hypovolemia in mechanically ventilated patients and in controlled laboratory environments. In this retrospective study, we investigated if PPG RIWV metrics have diagnostic value for patients with acute hemorrhagic hypovolemia in the prehospital environment. Photoplethysmogram waveforms and basic vital signs were recorded in trauma patients during prehospital transport. Retrospectively, we used automated algorithms to select patient records with all five basic vital signs and 45 s or longer continuous, clean PPG segments. From these segments, we identified the onset and peak of individual heartbeats and computed waveform variations in the beats' peaks and amplitudes: (1) as the range between the maximum and the minimum (max-min) values and (2) as their interquartile range (IQR). We evaluated their receiver operating characteristic (ROC) curves for major hemorrhage. Separately, we tested whether RIWV metrics have potential independent information beyond basic vital signs by applying multivariate regression. In 344 patients, RIWV max-min yielded areas under the ROC curves (AUCs) not significantly better than a random AUC of 0.50. Respiration-induced waveform variation computed as IQR yielded ROC AUCs of 0.65 (95% confidence interval, 0.54–0.76) and of 0.64 (0.51–0.75), for peak and amplitude measures, respectively. The IQR metrics added independent information to basic vital signs ($P < 0.05$), but only moderately improved the overall AUC. Photoplethysmogram RIWV measured as IQR is preferable over max-min, and using PPG RIWV may enhance physiologic monitoring of spontaneously breathing patients outside strictly controlled laboratory environments.

KEYWORDS—PPG waveform variation, hemorrhage, trauma, prehospital care

INTRODUCTION

Exsanguination is the singularly treatable mechanism of mortality for trauma casualties (1–4), and the earlier hemorrhagic hypovolemia is detected, the greater the opportunity exists for caregivers to administer volume replacement and/or surgically intervene. Recently, it has been suggested that photoplethysmography (PPG), which is a component of routine pulse oximetry, may be useful for detecting hypovolemia and hypotension (5–13). In a set of reports, metrics related to respiration-induced waveform variation (RIWV) of the PPG were associated with hypovolemia and hypotension for mechanically ventilated patients (5–11) and also for spontaneously breathing volunteer subjects during controlled laboratory protocols (12, 13). In these reports, the subjects were either cooperative or sedated, and the environmental conditions were relatively well controlled.

In this study, we examined the relationship between PPG RIWV and hypovolemia in patients transported by air ambulance after major trauma. We had two goals: (1) evaluate the univariate discriminatory value of PPG RIWV metrics for diagnosing hemorrhagic hypovolemia and (2) investigate the potential of PPG RIWV metrics to provide independent information above and beyond basic vital signs. If PPG RIWV metrics can be shown useful for detecting hypovolemia in a prehospital context, these metrics might be applicable to a wide range of clinical arenas in which environmental and physiologic factors are minimally controlled.

MATERIALS AND METHODS

Clinical data collection

This study was based on physiologic data collected from 898 trauma patients during medical helicopter transport between August 2001 and April 2004, from the scene of injury to the level I unit at the Memorial Hermann Hospital in Houston, Tex (14). The data were measured by Propaq 206EL transport monitors (Protocol Systems, Beaverton, Ore), downloaded to an attached personal digital assistant, and ultimately stored in our database (15). The variables consisted of electrocardiogram, PPG, and respiratory waveform signals recorded at 182, 91, and 23 Hz, respectively, and their corresponding monitor-calculated vital signs, recorded at 1-s intervals (heart rate [HR], oxygen saturation of arterial hemoglobin [SpO₂], and respiratory rate [RR]). In addition, systolic (SBP), mean, and diastolic (DBP) blood pressures were collected intermittently at multiminute intervals. Attribute data were collected retrospectively via chart review, including demographics, injury descriptions, prehospital interventions, and hospital treatments. There were 100 attribute parameters for each patient, and these data have undergone prior analysis (16–21). Investigational review board approval for the data collection was given by the Memorial Hermann Hospital and the US Army Medical Research and Materiel Command Office of Research Protection, Fort Detrick,

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Md. For this study, we obtained deidentified patient data from Memorial Hermann Hospital.

Inclusion criteria

Patients were selected for analysis based on the availability, within the first 25 min of transport, of (a) 45 s or longer continuous, clean PPG waveform data; (b) 45 s or longer continuous, nonzero HR, RR, and SpO_2 data; and (c) at least one SBP and DBP measurement. Patients without clean PPG waveform data or missing any one of the basic vital signs were excluded. Determination of clean PPG data segments was accomplished using a computer algorithm, which, in a prior report, yielded a high rate of agreement with human expert review about whether PPG waveform segments were clean (specifically, whether beats were deemed to be unambiguously identifiable by the reviewer), although the algorithm's performance was relatively more conservative, i.e., more specific, about what data were clean, relative to the human evaluators (22).

PPG waveform processing and measurement of RIWV

For each patient, metrics of PPG RIWV were computed using all continuous clean waveform segments of 45 s or longer that were identified in the aforementioned analysis. In each clean PPG waveform segment, we identified the onset and peak locations for each beat, using an automated computer algorithm that has been previously reported (23). The algorithm identifies PPG peaks as local maximal positions on the PPG waveform, and beat onsets as the nearest minimal position preceding each corresponding peak. Each beat's amplitude is defined as the difference in heights between a peak and its preceding onset (Fig. 1).

After identifying the peaks, onsets, and amplitudes of each beat in all continuous clean waveform segments of 45 s or longer, we then computed the investigative PPG metrics.

- First, we computed the difference between the maximum and the minimum (max-min) of the peak heights of all beats within a moving 45-s window and advanced the time window 15 s at a time within the clean PPG segments. We then averaged the max-min values over all time windows in the 25-min data record that contained clean PPG waveform data.
- The max-min of the amplitudes was computed in an analogous fashion, using a moving 45-s window and then averaging the max-min results from all eligible windows of each patient record.
- We also computed the differences between the first quartile and the third quartile values (the interquartile range [IQR]) for both the peak heights and the amplitudes within a moving 45-s window and then averaged the results from all eligible windows of each patient record.

Calculation of basic vital signs

For each of the five basic vital signs (HR, RR, SpO_2 , SBP, and DBP), we computed the average parameter value within the initial 25 min of data collection using the most reliable vital-sign measurements and excluding from calculation the less reliable data. Reliability was determined by automated algorithms that have been previously validated, which rate each vital-sign datum on an integer scale of 0 to 3, from least reliable to most reliable (16, 18, 22).

- When the HR algorithm identified reliable data, in 97% of the cases, blinded human experts concurred with the monitor's reported HR (22).
- Respiratory rate data determined to be reliable by the RR algorithm were statistically superior to the time average of all RR data, as a predictor of hospital intubation and of major hemorrhage (21).

- Reliable SBP, as determined by the blood pressure algorithm, was found to be statistically superior to unreliable SBP, as a predictor of major hemorrhage (20).
- As a predictor of major hemorrhage and mortality, the Revised Trauma Score (RTS) automatically computed from reliable RR and SBP data was superior to the RTS computed from less reliable RR and SBP data and was equivalent to the RTS based on medic documentation (16).
- For reliable SpO_2 , the positive predictive value increased from less than 75% (for conventional SpO_2 measurements) to more than 95% (for "reliable" SpO_2) as a predictor of in-hospital documentation of thoracic or intracerebral injury (20).

Definition of major hemorrhage (primary outcome)

The primary outcome was major traumatic hemorrhage, defined as patients who received one or more unit of packed red blood cell (PRBC) transfusion within 24 h upon arrival at the hospital and had a documented injury that was explicitly hemorrhagic, which was one or more of the following: (a) laceration or fracture of a solid organ, (b) thoracic or abdominal hematomas, (c) explicit vascular injury that required operative repair, or (d) limb amputation. In the primary analysis, patients who received blood but did not meet the documented injury criteria, i.e., ambiguous hemorrhagic patients, and patients who died before arrival at the hospital were excluded from the analysis (121 patients excluded). Alternative outcome definitions for major hemorrhage were explored in a set of secondary sensitivity analyses, described below.

Statistical methods

Univariate analysis—The diagnostic performances of the investigational PPG metrics were evaluated by constructing the receiver operating characteristic (ROC) curves and calculating the area under the curve (AUC) for each ROC curve. We used the ROCKIT freeware (University of Chicago, available at: http://xray.bsd.uchicago.edu/krl/KRL_ROC/software_index.htm) for these analyses (24). ROCKIT assumes a binormal ROC model, i.e., data for each of the decision outcomes (hemorrhage versus control) are considered to be normally distributed and the ROC parameters can be estimated based on the model assumption. The ROC curves calculated by this method are smoother than empirically evaluated ROC curves and can better represent the relationship between vital-sign variables and decision outcomes (24, 25). Using ROCKIT, we tested if each ROC was significantly different from chance, i.e., if the ROC AUC was significantly greater than 0.50. As a basis for interpreting the results, we also computed the ROC AUC of HR and SBP.

We also tested if the PPG metrics were correlated with the number of PRBC units transfused in the first 24 h.

Multivariate regression analysis—We used a linear multivariate regression routine "stepwisefit" in MATLAB (version 7.0; The MathWorks, Natick, Mass) to compare the discriminatory power of models with and without each investigational PPG metric, in addition to the five basic vital signs (i.e., HR, RR, SpO_2 , SBP, and DBP). The routine uses an F statistic to evaluate additional discriminatory power provided by the investigative PPG metric and decides whether the PPG metric should be included based on a significance threshold of $P < 0.05$.

In theory, prehospital fluids might obscure PPG RIWV in patients with major hemorrhage. To study if prehospital fluid administration was a major determinant of PPG metrics, we (a) computed the correlation between prehospital fluid volume and PPG RIWV metrics and (b) tested if both PPG metrics and fluid volume were independently correlated with major hemorrhage, in a multivariate regression model.

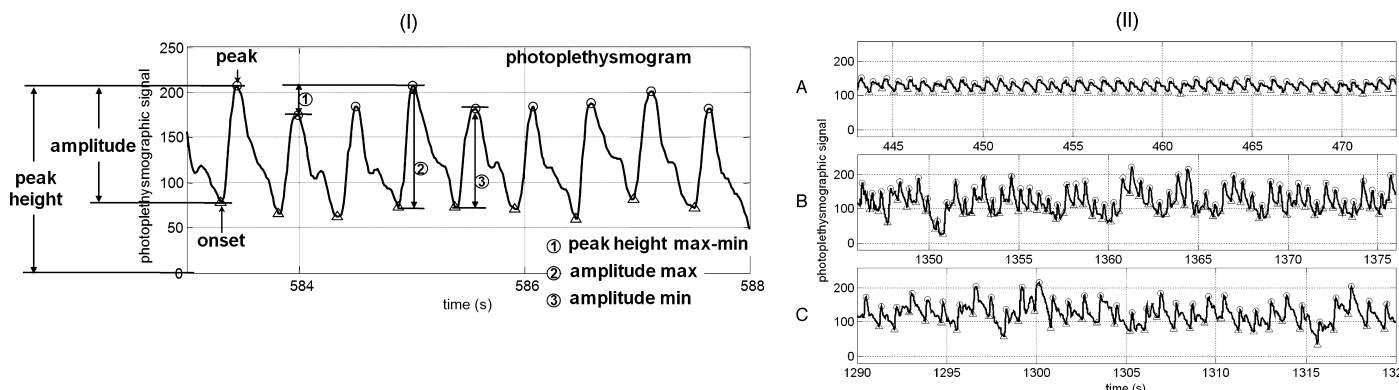


FIG. 1. Vascular beat onsets and peaks on the PPG. Panel I shows the derived peak height and amplitude metrics, and Panel II shows three exemplary PPG waveform segments from the database; PPG beat onsets and peaks were identified by an automated algorithm.

TABLE 1. Demographics of the study and the overall population

Characteristics	Overall database	Study population
Population size, n	898	344
Male	660* (73%)	266 (77%)
Female	234* (26%)	78 (23%)
Mean age, y	37 (16 [†])	37 (15 [†])
Blunt injury	778 (87%)	308 (90%)
Mortality	94 (10%)	13 (4%)
Prehospital intubated	201 (22%)	55 (16%)
Major respiratory intervention [‡]	102 (11%)	30 (9%)
Major hemorrhage [§]	94 (10%)	26 (8%)

We excluded 399 patients because they had no suitable PPG waveform data available, 121 because they received blood transfusion without an explicitly hemorrhagic injury, and 34 because they had one or more of the other basic vital signs unavailable; see text for further details of the exclusion criteria.

*Four patients had no assigned sex in the total population.

[†]SD.

[‡]Received major respiratory lifesaving interventions in the hospital, i.e., endotracheal intubation or chest tube insertion.

[§]Received blood transfusion in the hospital and also had documented injuries that were consistent with major hemorrhage.

Sensitivity analysis—We repeated the preceding computations using (a) exclusion of mechanically ventilated patients, (b) different PPG waveform segment lengths, (c) different PPG waveform quality criteria, (d) different definitions of major hemorrhage, and (e) scaling each PPG metric to the maximal amplitude within each 45-s waveform segment. In (b), we changed the PPG waveform length criteria to require continuous PPG waveforms of 30 s or longer or 60 s or longer. In (c), we relaxed our clean PPG waveform criterion and required only 90% or greater or 80% or greater clean waveform in each segment of 45 s or longer; this increased our population size. In (d), we repeated the calculations exploring alternative definitions of major hemorrhage: cases who received five or more units of PRBC and had documented injuries (massive hemorrhage); cases who received emergency red blood cell transfusions regardless of their injuries; and cases who received either red cell transfusions and/or 3 L or more in-hospital crystalloid, regardless of their injuries. Regarding (e), most PPG waveform outputs from a patient monitor are autoscaled (to compensate for factors such as tissue opacity and local vascularity that have a major effect on the light intensity measured by the pulse oximetry probe); we explored if rescaling the PPG RIWV metrics would improve their diagnostic performance.

RESULTS

The study population was similar to the total population in sex, age, injury type, and rates of major respiratory intervention and major hemorrhage, but with lower rates of mortality and

TABLE 3. Multivariate analysis of four PPG metrics (1–4) and the five basic vital signs for the diagnosis of major hemorrhage

No.	PPG metric	P*	Improvement of ROC AUC [†] with one additional PPG metric (compared with the basic linear model shown in the first row)
Linear model with five basic vital signs			0.79 (CI, 0.68–0.87)
1	Peak height max-min	NS	+0.00
2	Amplitude max-min	NS	+0.02
3	Peak height IQR	0.007	+0.02
4	Amplitude IQR	0.004	+0.03

*P value testing whether each PPG metric added significant amount of new information to the linear model.

[†]ROC AUC computed by the ROCKIT software (University of Chicago). NS indicates not statistically significant.

prehospital intubation (Table 1). The investigative IQR PPG metrics generated ROC AUCs of 0.64 or greater, significantly greater than 0.50 (Table 2). The two max-min metrics generated nonsignificant discriminatory power, with ROC AUC 95% confidence intervals (CIs) for the AUCs spanning 0.50.

The PPG metrics were weakly correlated with the PRBC transfusion requirement. For instance, the correlation (*r*) between PPG peak height IQR versus the units of PRBCs transfused was 0.14 (*P* < 0.01) for all patients. Looking exclusively at the 26 patients with one or more unit of PRBC, there was a trend toward higher correlation, *r* = 0.39, but because there were fewer patients, this was not a significant finding (*P* = 0.06).

The two IQR PPG metrics were both significant independent correlates (*P* < 0.01) of major hemorrhage in a multivariate regression model that also included all five basic vital signs (Table 3). However, per ROCKIT, the resultant improvements in ROC AUC (by +0.02 and +0.03, when either one of the two metrics was separately added to a linear model that also included all five basic vital signs) were not significant. Moreover, adding them into the linear model did not further improve the ROC AUC. These two IQR PPG metrics correlated significantly with each other (correlation coefficient = 0.80, *P* < 0.0001).

Based on the Youden (26) criterion, the peak height IQR metric had an optimal univariate sensitivity of 0.54 and a specificity of 0.73 (Fig. 2, left and right panels, line a). The five

TABLE 2. Univariate analysis of the association between four PPG metrics (1–4), HR (5), and SBP (6) with major hemorrhage

No.	PPG metric	Control, mean (SD)	Hemorrhage, mean (SD)	Student <i>t</i> test <i>P</i>	ROC AUC* (CI [†])
1	Peak height max-min	101 (42)	115 (38)	NS	0.60 (0.48–0.71)
2	Amplitude max-min	76 (40)	85 (40)	NS	0.57 (0.45–0.68)
3	Peak height IQR	24 (12)	31 (14)	0.01	0.65 (0.54–0.76)
4	Amplitude IQR	15 (7)	19 (8)	0.01	0.64 (0.51–0.75)
5	HR	92 (18) bpm	100 (19) bpm	0.048	0.62 (0.50–0.73)
6	SBP	134 (22) mmHg	115 (23) mmHg	<0.001	0.75 (0.65–0.84)

*ROC AUC computed by the ROCKIT software (University of Chicago).

[†]95% confidence interval.

NS indicates not statistically significant.

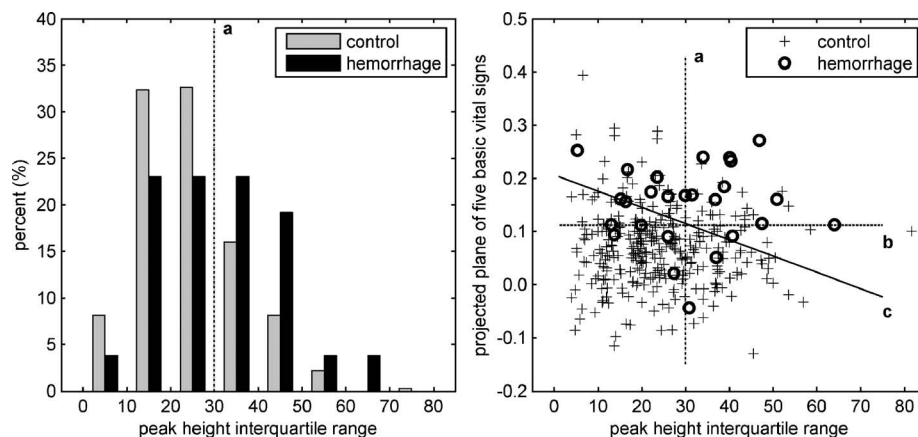


FIG. 2. Discrimination of major hemorrhage using peak height IQR as a univariate predictor (left) and its combination with five basic vital signs as a multivariate predictor (right). Lines a, b, and c show the optimal decision thresholds based on the Youden criterion.

basic vital signs had an optimal sensitivity of 0.77 and specificity of 0.76 (Fig. 2, right panel, line b). The optimal point for the multivariate model that included the peak height IQR metric and the basic vital signs yielded a sensitivity of 0.73 and a specificity of 0.82 (Fig. 2, right panel, line c). The amplitude IQR metric yielded similar results.

In our data set, patients with major hemorrhage received more total prehospital fluid than control patients (median, 850 [IQR, 500–1,200] mL and 250 [IQR 100–500] mL, respectively). However, total volume of prehospital fluid was not correlated with PPG metrics ($P > 0.05$) for neither hemorrhage patients nor control patients. In multivariate regression, PPG metrics and prehospital fluid volume were both independently associated with major hemorrhage ($P < 0.01$ for both). Therefore, administration of prehospital fluids did not

seem to alter the utility of PPG RIWV for identifying patients with major hemorrhage.

Sensitivity analyses

We verified that PPG RIWV metrics had relatively stable diagnostic performances even when we explored alternative analysis methodologies (Table 4). Exclusion of mechanically ventilated patients did not significantly change the ROC AUCs (changing by +0.01 and –0.02). When we selected cases and controls with longer and cleaner PPG segments, fewer patients were available, whereas, conversely, selecting for shorter and less clean PPG segments increased the number of eligible patients. Overall, changing the length of the PPG waveform segments (i.e., changing our inclusion/exclusion criteria) did not improve the ROC AUCs. Photoplethysmogram RIWV

TABLE 4. Sensitivity analysis of PPG metrics

No.	Exclusion of ventilated patients	PPG length, s	PPG waveform, % clean	Hemorrhage criteria	Scaled to max amplitude	Population		ROC AUC*	
						Control	Hemorrhage	Peak height IQR	Amplitude IQR
P	No	45	100	Dx [†] + PRBC	No	318	26	0.65 [‡]	0.64 [‡]
1	Yes	45	100	Dx + PRBC	No	270	19	0.66 [‡]	0.62
2	No	30	100	Dx + PRBC	No	382	31	0.62 [‡]	0.57
3	No	60	100	Dx + PRBC	No	270	21	0.62	0.60
4	No	45	90	Dx + PRBC	No	359	28	0.63	0.61
5	No	45	80	Dx + PRBC	No	397	34	0.61	0.57
6	No	45	100	Dx + 5 PRBC	No	318	10	0.71 [‡]	0.69 [‡]
7	No	45	100	PRBC or 3 L[§]	No	284	90	0.57	0.59 [‡]
8	No	45	100	PRBC	No	318	56	0.56	0.56
9	No	45	100	Dx + PRBC	Yes	318	26	0.59	0.63 [‡]

P restates the primary analysis and results (from Table 2). In analyses 1 to 5, we varied the inclusion criteria: whether ventilated patients were included, the minimal duration of PPG segments analyzed, and the minimal proportion of clean waveform of PPG segments analyzed. Note that when selecting for cases and for controls with longer and cleaner PPG segments, fewer patients are available. In analyses 6 to 8, we varied the definition of our outcome: major hemorrhage: receipt of five or more units of PRBCs and with documented injuries (massive hemorrhage), no requirement for explicit documentation of a hemorrhagic injury, and inclusion of patients with 3 L or more in-hospital crystalloid. Bold font is used to highlight the different conditions within each group of analysis. In analysis 9, we rescaled the PPG waveform before computing the investigational RIWV metrics; see text for further details.

*ROC AUC computed by the ROCKIT software (University of Chicago).

[†]Documented anatomic injuries (Dx).

[‡]AUC significantly greater than 0.5 ($P < 0.05$).

[§]In-hospital crystalloid 3 L or more.

metrics were able to identify patients with massive hemorrhage (≥ 5 U of PRBCs transfused) at least as well as the primary definition. However, alternative definitions of major hemorrhage without requiring formal documentation of a hemorrhagic injury yielded a trend toward reduced ROC AUCs. Rescaling the PPG waveform did not improve the ROC AUCs.

DISCUSSION

This study demonstrates that PPG RIWV is associated with hemorrhagic hypovolemia in a minimally controlled clinical arena, i.e., immediately after major mechanism trauma in patients with varying degrees of pain, anxiety, head injury, chest injury, alcohol intoxication, confusion, and so on, although its discriminatory value is not great (ROC AUC generally <0.70). The methodology of using PPG RIWV is appealing because measurement of PPG RIWV is strictly noninvasive, and the necessary instrumentation (in the form of the familiar pulse oximeter) is essentially ubiquitous in most health care environments. Therefore, as an alternative approach for detecting hypovolemia, it would be relatively easy to disseminate. (Indeed, pulse oximeters that display metrics of waveform variation are already commercially available (27).) Our multivariate analysis suggested that PPG RIWV metrics may be independent predictors of major hemorrhage ($P < 0.01$) above and beyond SBP, DBP, HR, RR, and SpO_2 , although the added benefit was incremental (raising the ROC AUC $+0.03$). Photoplethysmogram RIWV metrics could therefore be useful in conjunction with other vital signs for patient monitoring, perhaps as an input to computerized multiparameter alarm algorithms [such algorithms have been described by Imhoff and Kuhls (28), Chen et al. (17), and Tarassenko et al. (29)].

For our four investigative PPG metrics, we found that AUCs spanned from 0.57 to 0.65 (CIs from 0.45–0.76), which, considering the enormous variability of prehospital patients and their environments, was still somewhat less than what has been reported from an intensive care unit (ICU) setting during mechanical ventilation for the identification of volume-responsive patients (ROC AUC of 0.72) (13). We found that PPG peak height IQR yielded the highest AUC of our investigative metrics and was moderately sensitive (54%) at its optimal threshold, whereas its positive predictive value was less than 20%. These results do not support the use of PPG RIWV metrics for stand-alone hemodynamic monitoring. However, when PPG RIWV metrics are distinctly elevated, it would be prudent to carefully evaluate the patient, just as prudence is appropriate when HR is elevated.

Before this analysis, it was not obvious that PPG RIWV would be associated with hemorrhage in a spontaneously breathing prehospital population. The association between PPG RIWV and volume-responsive states has been mainly documented in mechanically ventilated patients (5–11), where it was found to be an analog of pulsus paradoxus, i.e., respiration-induced variability of arterial blood pressure (7, 30). Because the PPG signal is highly prone to motion artifacts caused by even minor movements of the pulse oximeter probe, an operating room (OR) or ICU is arguably the optimal clinical environment for making PPG measurements, because the patients, sedated or paralyzed, are stationary. Also,

mechanical ventilation offers a controllable and consistent respiratory stimulus; in theory, monitoring PPG RIWV might be less effective in spontaneously breathing patients, given their wider range of breathing patterns [respiratory effort is another major determinant of PPG RIWV; e.g., see Rayner et al. (31)]. We are unaware of any prior reports of this association for clinical arenas as poorly controlled as the prehospital air ambulance.

We did find that a suitably clean PPG signal was often unavailable (44%) in our prehospital population, which would limit the clinical usefulness of these PPG metrics in this population. The patients with available PPG data tended to be less sick, versus the overall population (Table 1). For some of the higher-acuity patients, the medics may have fewer opportunities to tend to a noisy PPG signal, or the PPG signal (which is a function of skin perfusion) may have been fainter. Note that novel PPG probe designs, for different anatomic measurement locations, have been described to reliably measure the PPG signal in ambulatory patients (32) or after a mass casualty event (33). Ultimately, enhancement of pulse oximetry instrumentation, to obtain a reliable signal in most patients and to reduce motion artifacts, may be necessary for operational applications involving PPG RIWV metrics in minimally controlled settings.

In the multivariate analysis, PPG RIWV metrics were significant independent predictors of major hemorrhage, even though the increases in ROC AUC were nonsignificant. Nonsignificance can mean that there is no true effect, or it can mean that the effect is too small to be identified, given our sample size. Because the multivariate regression convincingly suggested an independent relationship between PPG RIWV and major hemorrhage ($P < 0.01$), we interpret our results to mean that there was, in fact, an independent association between PPG RIWV, but its discriminatory power was simply too weak to be identified in our study population.

Limitations

It is possible that our findings were dependent on our specific algorithm for measuring RIWV. However, in a prior brief report, we performed a human overread of 4,605 different PPG beats processed by this algorithm and identified only 15 points in which the algorithm incorrectly identified the takeoff or peak of any apparent PPG pulse (23). In this current report, our analysis was made more rigorous by analyzing a minimum of 45 s of data and computing their IQR for two of the investigative metrics. Both these steps made our final results less affected if any individual PPG beats were incorrectly analyzed, i.e., individual outlier beats whose peak or amplitude was incorrectly computed. Another advantage of this automated methodology is that it was entirely objective. Shamir et al. (5) relied on less objective hand measurements of paper recordings of the PPG waveform, whereas Golparvar et al. (6) videotaped the PPG waveform and then measured the investigational PPG metrics in units of pixels of a video display. We contend that, overall, our automated methodology is a strength of our study. Alternative computational methods would probably yield slightly different results, but we argue that it is unlikely that any other computational method would

substantially alter our findings. Our ROC AUCs were only moderately less than those previously reported for detecting hypovolemia in paralyzed, mechanically ventilated intraoperative patients (13).

The second question is if our ROC AUCs results are generalizable beyond the prehospital air ambulance, which may be unique in its incidence of motion, pain, hypothermia, and so on. Broadly speaking, different populations will have different incidences of confounding conditions. For example, a population with more respiratory pathology, e.g., asthma, would presumably have more cases of increased RIWV regardless of intravascular volume (31). Questions about how to best measure the PPG signal in uncontrolled clinical arenas, as well as the generalizability of our results, can be clearly answered only with future, broader clinical studies. We speculate that many clinical arenas (e.g., post-acute-care units, medical-surgical inpatient wards, etc.) will end up yielding ROC AUCs somewhere between our results, which may represent the lower end of clinical control, and AUCs from ICU trials with mechanically ventilated patients [e.g., see Natalini et al. (13)], which represent the highest levels of clinical control.

CONCLUSIONS

In prehospital trauma casualties, a significant univariate association between PPG RIWV and major hemorrhage was found. The ROC AUCs were comparable to that of HR, which suggests that they may have value for monitoring spontaneously breathing patients outside the OR, but not necessarily as a sole monitoring modality. In a multivariate analysis including basic vital signs, PPG RIWV metrics showed significant independent correlations with major hemorrhage. Photoplethysmogram RIWV metrics may enhance novel patient monitoring and automated multiparameter alarm algorithms outside the controlled environment of the OR and ICU.

REFERENCES

- Peng R, Chang C, Gilmore D, Bongard F: Epidemiology of immediate and early trauma deaths at an urban level I trauma center. *Am Surg* 64(10):950–954, 1998.
- Sauaia A, Moore FA, Moore EE, Moser KS, Brennan R, Read RA, Pons PT: Epidemiology of trauma deaths: a reassessment. *J Trauma* 38(2):185–193, 1995.
- Carrico CJ, Holcomb JB, Chaudry IH: Scientific priorities and strategic planning for resuscitation research and life saving therapy following traumatic injury: report of the PULSE Trauma Work Group. Post Resuscitative and Initial Utility of Life Saving Efforts. *Shock* 17(3):165–168, 2002.
- Rossaint R, Cerny V, Coats TJ, Duranteau J, Fernandez-Mondejar E, Gordini G, Stahel PF, Hunt BJ, Neugebauer E, Spahn DR: Key issues in advanced bleeding care in trauma. *Shock* 26(4):322–331, 2006.
- Shamir M, Eidelman LA, Floman Y, Kaplan L, Pizov R: Pulse oximetry plethysmographic waveform during changes in blood volume. *Br J Anaesth* 82(2):178–181, 1999.
- Golparvar M, Naddafnia H, Saghaei M: Evaluating the relationship between arterial blood pressure changes and indices of pulse oximetric plethysmography. *Anesth Analg* 95(6):1686–1690, 2002.
- Cannesson M, Besnard C, Durand PG, Bohe J, Jacques D: Relation between respiratory variations in pulse oximetry plethysmographic waveform amplitude and arterial pulse pressure in ventilated patients. *Crit Care* 9(5):R562–R568, 2005.
- Cannesson M, Desebbe O, Hachemi M, Jacques D, Bastien O, Lehot JJ: Respiratory variations in pulse oximeter waveform amplitude are influenced by venous return in mechanically ventilated patients under general anaesthesia. *Eur J Anaesthesiol* 24(3):245–251, 2007.
- Cannesson M, Desebbe O, Rosamel P, Delannoy B, Robin J, Bastien O, Lehot JJ: Pleth variability index to monitor the respiratory variations in the pulse oximeter plethysmographic waveform amplitude and predict fluid responsiveness in the operating theatre. *Br J Anaesth* 101(2):200–206, 2008.
- Gesquiere MJ, Awad AA, Silverman DG, Stout RG, Jablonka DH, Silverman TJ, Shelley KH: Impact of withdrawal of 450 ml of blood on respiration-induced oscillations of the ear plethysmographic waveform. *J Clin Monit Comput* 21(5):277–282, 2007.
- Cannesson M, Sliker J, Desebbe O, Bauer C, Chiari P, Henaine R, Lehot JJ: The ability of a novel algorithm for automatic estimation of the respiratory variations in arterial pulse pressure to monitor fluid responsiveness in the operating room. *Anesth Analg* 106(4):1195–1200, 2008.
- Delorme S, Renault R, Le Manach Y, Lvovschi V, Bendahou M, Riou B, Ray P: Variations in pulse oximetry plethysmographic waveform amplitude induced by passive leg raising in spontaneously breathing volunteers. *Am J Emerg Med* 25(6):637–642, 2007.
- Natalini G, Rosano A, Taranto M, Faggian B, Vittorielli E, Bernardini A: Arterial versus plethysmographic dynamic indices to test responsiveness for testing fluid administration in hypotensive patients: a clinical trial. *Anesth Analg* 103(6):1478–1484, 2006.
- Cooke WH, Salinas J, Convertino VA, Ludwig DA, Hinds D, Duke JH, Moore FA, Holcomb JB: Heart rate variability and its association with mortality in prehospital trauma patients. *J Trauma* 60(2):363–370, 2006.
- McKenna TM, Bawa G, Kumar K, Reifman J: The physiology analysis system: an integrated approach for warehousing, management and analysis of time-series physiology data. *Comput Methods Programs Biomed* 86(1):62–72, 2007.
- Reisner AT, Chen L, McKenna TM, Reifman J: Automatically-computed prehospital severity scores are equivalent to scores based on medic documentation. *J Trauma* 65(4):915–923, 2008.
- Chen L, McKenna TM, Reisner AT, Gribok A, Reifman J: Decision tool for the early diagnosis of trauma patient hypovolemia. *J Biomed Inform* 41:469–478, 2008.
- Chen L, McKenna TM, Reisner AT, Reifman J: Algorithms to qualify respiratory data collected during the transport of trauma patients. *Physiol Meas* 27(9):797–816, 2006.
- Chen L, Gribok A, Reisner AT, Reifman J: Exploiting the existence of temporal heart-rate patterns for the detection of trauma-induced hemorrhage. *Conf Proc IEEE Eng Med Biol Soc* 2008:2865–2868, 2008.
- Chen L, Reisner AT, Gribok A, Reifman J: Exploration of prehospital vital sign trends for the prediction of trauma outcomes. *Prehosp Emerg Care* 13(3):286–294, 2009.
- Chen L, Reisner AT, Gribok A, McKenna TM, Reifman J: Can we improve the clinical utility of respiratory rate as a monitored vital sign? *Shock* 31(6):574–580, 2009.
- Yu C, Liu Z, McKenna T, Reisner AT, Reifman J: A method for automatic identification of reliable heart rates calculated from ECG and PPG waveforms. *J Am Med Inform Assoc* 13(3):309–320, 2006.
- Chen L, Reisner AT, Reifman J: Automated beat onset and peak detection algorithm for field-collected photoplethysmograms. *Conf Proc IEEE Eng Med Biol Soc* 2009:5689–5692, 2009.
- Metz CE, Herman BA, Shen JH: Maximum likelihood estimation of receiver operating characteristic (ROC) curves from continuously-distributed data. *Stat Med* 17(9):1033–1053, 1998.
- Obuchowski NA: ROC analysis. *Am J Roentgenol* 184(2):364–372, 2005.
- Youden WJ: Index for rating diagnostic tests. *Cancer* 3(1):32–35, 1950.
- Cannesson M, Delannoy B, Morand A, Rosamel P, Attouf Y, Bastien O, Lehot JJ: Does the Pleth variability index indicate the respiratory-induced variation in the plethysmogram and arterial pressure waveforms? *Anesth Analg* 106(4):1189–1194, 2008.
- Imhoff M, Kuhls S: Alarm algorithms in critical care monitoring. *Anesth Analg* 102(5):1525–1537, 2006.
- Tarassenko L, Hann A, Young D: Integrated monitoring and analysis for early warning of patient deterioration. *Br J Anaesth* 97(1):64–68, 2006.
- Westphal GA, Silva E, Caldeira Filho M, Roman Goncalves AR, Poli-de-Figueiredo LF: Variation in amplitude of central venous pressure curve induced by respiration is a useful tool to reveal fluid responsiveness in post-cardiac surgery patients. *Shock* 26(2):140–145, 2006.
- Rayner J, Trespalacios F, Machan J, Potluri V, Brown G, Quattrucci LM, Jay GD: Continuous noninvasive measurement of pulsus paradoxus complements medical decision making in assessment of acute asthma severity. *Chest* 130(3):754–765, 2006.
- Asada HH, Shaltis P, Reisner A, Rhee S, Hutchinson RC: Mobile monitoring with wearable photoplethysmographic biosensors. *IEEE Eng Med Biol Mag* 22(3):28–40, 2003.
- Wendelken SM, McGrath SP, Akay M, Blike GT: Using a forehead reflectance pulse oximeter to detect changes in sympathetic tone. *Conf Proc IEEE Eng Med Biol Soc* 1:325–328, 2004.